Remarks

Claims 34 and 41-44 are pending. Claims 48 has been added. Support for new claim 48 is found, for example, on page 1, lines 3-5; and page 39, lines 1-3.

Rejection Under 35 U.S.C. § 103

Claims 34 and 41-44 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Friedlos *et al., Biochemical Pharmacology*, 44(1), 25-31, (1992) ("Friedlos"), in view of Norris *et al., Can. J. Chem.*, Vol. 55, 1687-1695 (1977) ("Norris"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998)

(The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

The Claimed Invention is Not Obvious

Claim 34 recites a therapeutic system comprising a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 and a compound of formula I wherein the compound can pass reducing equivalents to NQO2, in a form for administration to a patient in need thereof, wherein the prodrug is CB 1954.

The claims are directed to a therapeutic system. The therapeutic effect is, therefore, a feature of the claimed subject matter. A therapeutic system may, for example, be labeled for a particular therapeutic application and/or include information about dosages on any packaging. A therapeutic system does not simply define a mixture of two or more compounds but includes the

technical feature of a therapeutic effect, which may be in the form of additional technical information relating to a therapeutic application, but must include being in an effective dosage and in a formulation suitable for administration to a person in need, unlike in a typical research laboratory or *in vitro* testing. The compounds specified in claim 34 are useful in therapy, particularly in the treatment of tumors that express NQO2.

Friedlos

Friedlos describes reduced pyridinium derivatives as synthetic cofactors in the reduction of CB 1954 by the enzyme DT diaphorase. (page 28, 1st column, last paragraph and Table 1). Friedlos does not disclose or even suggest that the combination of an analogue of NRH and CB 1954, as claimed, could be used as a system for any type of therapy let alone the treatment of tumors which express NQO2. Friedlos is concerned with the use of reduced pyridinium derivatives as cofactors for the reduction of quinine, menadione, or CB 1954 by DT diaphorase. The only suggested application of the cofactors is in the *in vitro* biochemical study of DT diaphorase and in particular in the histochemical staining and location of DT diaphorase (page 30, right hand column, final 12 lines).

The claimed systems are based, at least in part, on the recognition that an analogue of NRH, as claimed, acts in conjunction with *NQO2*, not DT diaphorase. DT diaphorase is a distinctly different enzyme from NQO2 (page 8, lines 18-21). The motivation for using an analogue of NRH, as claimed, in combination with CB 1954 in a therapeutic system could only

have become apparent after the role of NQO2 had been recognized (page 46, lines 19-23). Friedlos does not recognize the role of NQO2.

The Examiner refers to page 28 and Table 1 in Friedlos as disclosing cofactors of CB 1954. However, this disclosure relates to cofactors for *menadione*, not CB 1954. The Examiner goes on to state that cofactor requirements for DT diaphorase are fairly lax insofar as the adenine nucleoside portion of NAD(P)H is concerned. Friedlos states that "[t]hus, the simplest quaternary (and therefore reducible) derivative of nicotinamide, 1-methylnicotinamide, was as good a cofactor as NAD(P)H for the reduction of menadione by *DT diaphorase* not NQO2. Friedlos does not refer to CB 1954.

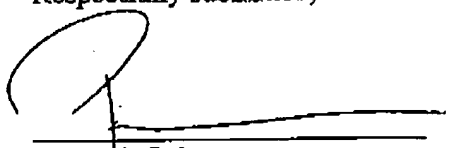
Friedlos indicates separately that the apparent K_m values for all of the cofactors with CB 1954 appeared to be approaching zero so that nicotinamide ribotide was apparently just as good a co-factor for the reduction of CB 1954 as NADH (page 29, right column, first full paragraph, final five lines). However, due to the particular kinetics underlying the operation of DT diaphorase, the K_m values are actually an artifact (page 30, left column, line 25 to page 30, second column, line 1). Thus, not all of the cofactors, in reality, have the same activity. This is demonstrated by using a mixture of NADH and nicotinamide ribotide wherein all of the NADH is oxidized preferentially over nicotinamide ribotide during the reduction of CB 1954 (page 30, left column, line 25 to page 30, second column, line 1). Therefore, there is no disclosure or suggestion in Friedlos that the simplest quaternary derivatives would actually be as effective as NADH for the reduction of CB 1954 in the presence of DT diaphorase, let alone NQO2.

Norris

Norris teaches the identification and synthesis of pyridinium and dihydropyridine compounds which do not contain the adenine nucleotide portion of NADH (page 1687, 2nd column, 1st paragraph and Table 3). Norris does not disclose or suggest the combination of an analogue of NRH and CB 1954, as claimed, could be used as a system for any type of therapy let alone the treatment of tumors which express NQO2. Since Friedlos discloses that the naturally occurring compound, NADH, is effective for the reduction of CB 1954 by DT diaphorase and that NADH will be used preferentially over other cofactors, there would appear to be no benefit from the use of other cofactors, such as those described in Norris, in a therapeutic system. In fact, such a compound would have appeared to be redundant to one of ordinary skill in the art and thus there would be no expectation of success. One of ordinary skill in the art would not be motivated to combine Friedlos and Norris in order to arrive at the claimed therapeutic systems. Accordingly, the claims, as amended, are not obvious over Friedlos in view of Norris.

Allowance of claims 34, 41-44, and 48, as amended, is respectfully solicited.

Respectfully submitted,



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